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AMENDMENTS TO THE DRAWINGS

The attached sheet(s) of drawings includes changes to Figure 3 .

Attachment: Replacement sheet

REMARKS

Claims 22 and 23 are currently pending in the application. Claim 22 has been amended, Claim 23 has been canceled and Claim 49 has been added. Claims 1-21 and 24-48 have been withdrawn without prejudice. Although Applicants have withdrawn Claims 1-21 and 24-48 herein, they respectfully reserve the right to prosecute identical or similar Claims in this, or a related application. The specific grounds for rejection and Applicant's response to them are set forth in detail below.

1. The disclosure is objected to because of the following informalities:

> The Examiner states,"The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.
>
> The following title is suggested: A method of screening a compound for regulating a SGLT homolog.
>
> Appropriate correction is required."

Applicant has amended the title in the specification as suggested by the Examiner.

2. The drawing for Figure 3 is objected to because each of the panels is, black. The Examiner is unable to discern the data represented therein.

> The Examiner states, "Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application."

Applicant is concurrently submitting a "Replacement Sheet" for Figure 3 of the application. Examiner is requested to please see the "Attachment". The "Replacement Sheet" contains discernable data therein.

3. Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> The Examiner states,"Claim 22 is drawn to a method of screening a compound that regulates glucose uptake activity of "a" Na+/glucose transporter homolog in the small intestine comprising using the homolog. Claim 23 recites the Na+/glucose transporter (SGLT) homolog is a protein comprising the same or substantially the same amino acid sequence represented by SEQ ID NO:1, SEQ ID NO: 3, SEQ ID NO:5 or SEQ ID NO:50, its partial peptide, or a salt thereof.
>
> Specifically, the specification teaches that the Na+/glucose transporter (SGLT) homologs may be any protein derived from any cells of human and warm-blooded animals ... (page 8 lines 23-25). In addition, "substantially the same amino acid sequence" is used to mean an amino acid sequence having at least 70% homology, preferably at least about 80% more preferably at least about 90% homology, and most preferably at least about 95% homology to the amino acid sequence to be compared (page 9, lines 6-10). Moreover, the specification discloses that where the amino acid sequence is inserted, deleted, or substituted as described. above the position of its insertion, deletion, or substitution is not particularly limited (page 10, lines 14-16). Furthermore, the specification discloses that the partial peptide of the protein used in the present invention may be any peptide as long as it is a partial peptide of the protein used in the present invention and preferably has the property equivalent to that of the protein used in the present invention (page 11, lines 12-15). Finally, the specification teaches the peptides which are preferably used include peptides having sequences of at least 20, preferably at least 50, more preferably at least 70, much more preferably at least 100, and most preferably at least 200 amino acids, in the constituent amino acid sequence of the protein used in the present invention, and the like (page 11, lines 15-20). Thus, the Examiner has broadly interpreted claims 22 and 23 as reading upon any SGLT protein, including variants, derivatives, and fragments of the amino acid sequence of SEQ ID NO:1.
>
> Claims 22 and 23 are genus claims. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Specifically, the specification does not clearly define homolog, variants, derivatives, or fragments of the amino acid of SEQ ID NO:1 and all methods of using such.
>
> Thus, the scope of the claims includes numerous structural and functional variants, and the genus' are highly variant because a significant number of

structural and functional differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish (1) SGLT homologs from other SGLT homologs and (2) variants, derivatives, and fragments of the amino acid of SEQ ID NO: 1 from other variants and fragments of amino acid of SEQ ID NO:1 are missing from the disclosure. No common attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, homologs, variants, derivatives, and fragments of an amino acid of SEQ ID NO:1 are insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus for SGLT homologs, as well as variants and fragments of an amino acid of SEQ ID NO:1 and all methods of using such.

There is no description of the special features, which are critical to the structure and function of the genus claimed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the SGLT homologs and variants, derivatives, and fragments of the amino acid of SEQ ID NO:1 encompassed by the limitations. Thus, no identifying characteristics or properties of the claimed SLGT homolog or amino acid of SEQ ID NO:1 are provided such that one of skill would be able to predictably identify the encompassed variant biological and chemical entities recited in the instant claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a compound that suppresses the glucose uptake activity of the SGLT homolog comprising the amino acid sequence of SEQ ID NO: 1, does not

reasonably provide enablement for a method of screening a compound that regulates the glucose uptake activity of a Na+/glucose transporter (SGLT) homolog or a protein comprising the same of substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO:1 in the small intestine comprising the homolog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Nature of the invention and breath of the claims

The invention is drawn to a method of screening a compound that regulates the glucose uptake activity of a Na+/glucose transporter (SGLT) homolog or a protein comprising the same of substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO:1 in the small intestine comprising the homolog. The invention is broad because the recitation of claims 22 and 23 encompasses a large number of polypeptides.

Specifically, the specification teaches that the Na+/glucose transporter (SGLT) homologs may be any protein derived from any cells of human and warm-blooded animals ... (page 8 lines 23-25). In addition, "substantially the same amino acid sequence" is used to mean an amino acid sequence having at least 70% homology, preferably at least about 80% more preferably at least about 90% homology, and most preferably at least about 95% homology to the amino acid sequence to be compared (page 9, lines 6-10).

Moreover, the specification discloses that where the amino acid sequence is inserted, deleted, or substituted as described above the position of its insertion, deletion, or substitution is not particularly limited (page 10, lines 14-16).

Furthermore, the specification discloses that the partial peptide of the protein used in the present invention may be any peptide as long as it is a partial peptide of the protein used in the present invention and preferably has the property equivalent to that of the protein used in the present invention (page 11, lines 12-15). Finally, the specification teaches the peptides which are preferably used include peptides having sequences of at least 20, preferably at least 50, more preferably at least 70, much more preferably at least 100, and most preferably at least 200 amino acids, in the constituent amino acid sequence of the protein used in the present invention, and the like (page 11, lines 15-20). Thus, the Examiner has broadly interpreted claims 22 and 23 as reading upon any SGLT protein, including variants, derivatives, and fragments of the amino acid sequence of SEQ ID NO:1.

Unpredictability and state of the art

The state of the art for SGLT1 and SGLT2 is well known, but the state of the art for the full length and homologs, variants, derivatives, or fragments of the amino acid of SEQ ID NO: 1 is not well characterized.

Several studies have structurally and functionally characterized several members of the SGLT family. For instance, Zhou et al. (2003) teach that since both SGLT1 and SGLT2 play vital roles in absorption of glucose from both the small intestine and kidney, it is logical to speculate that the inhibitors of SGLT may have medical utilities for the treatment of diabetes (page 340, left column, 1st paragraph). Moreover, Scheepers et al. (2004) teach the secondary structure for the members of the SGLT family is based on the experimental studies of SGLT1 and related family members (page 364, right column, bottom paragraph). In addition, Scheepers et al. teach al. (2004) that intestinal glucose absorption and renal reabsorption in proximal tubules via SGLT1 and SGLT2 can be blocked by phlorizin, a plant product from the bark of the apple tree (page 365, left column, top paragraph).

However, the art is silent regarding the full length or derivatives for the SGLT homolog of SEQ ID NO:1. In the specification, Applicant teaches that based on the search for Gene Logic database, SGLT homolog is an important transporter for absorption of glucose in the small intestine (page 3, lines 5-7), but does not disclose any distinguishing characteristics for derivatives or fragments of the SGLT homolog. The variants, derivatives, or fragments of the amino acid of SEQ ID NO: 1 are not well characterized in the specification or the state of the art. Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from SEQ ID NO:1 while retaining the ability of the claimed polypeptide to transport glucose.

The variants, derivatives, or fragments of the SGLT homolog are not well characterized in the specification. Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from the claimed polypeptide while retaining the ability of the claimed glucose uptake. For instance, the specification teaches that where the amino acid sequence is inserted, deleted, or substituted as described above the position of its insertion, deletion, or substitution is not particularly limited (page 10, lines 14-16) encompassing an infinite number of changes to SEQ ID NO: 1. Each amino acid change to the SGLT homolog results in distinct structure, function, and biological activity, and the combination of any of these amino acid changes may result in distinct SGLT homolog characteristics. The teachings in the specification provide general characteristics of these domains but the specification does not provide any distinguishing or specific characteristics for any of these SGLT homolog variants required for a method for screening a compound.

Because applicant has not provided any distinguishing characteristics for any of the variants and fragments are not predictable for any of SGLT polypeptide homologs comprising any mutation, deletions, substitutions, or fragments. Undue experimentation would be required of one skilled in the art to be able to make/use the claimed methods of the instant application.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it-is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and

function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In view of these teachings in the art and the limited guidance provided in the specification, a method of screening a compound that suppresses the glucose uptake activity of SGLT homolog of SEQ ID NO:1 is not predictable for a method of screening a compound that regulates the glucose uptake activity of a Na+/glucose transporter (SGLT) homolog or a protein comprising the same of substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO:1 in the small intestine comprising the homolog.

The amount of direction or guidance present

Applicants' disclosure is limited to the structural description of the full-length amino acid of SEQ ID NO:1. However, the specification does not provide guidance or direction regarding all possible SGLT homologs and variants, derivatives, or fragments of the amino acid sequence of SEQ ID NO:1. The specification teaches that the Na+/glucose transporter (SGLT) homologs may be any protein derived from any cells of human and warm-blooded animals ... (page 8 lines 23-25). In addition, "substantially the same amino acid sequence" is used to mean an amino acid sequence having at leat 70% homology, preferably at least about 80% more preferably at least about 90% homology, and most preferably at least about 95% homology to the amino acid sequence to be compared (page 9, lines 6-10). Moreover, the specification discloses that where the amino acid sequence is inserted, deleted, or substituted as described above the position of its insertion, deletion, or substitution is not particularly limited (page 10, lines 14-16).

Furthermore, the specification discloses that the partial peptide of the protein used in the present invention may be any peptide as long as it is a partial peptide of the protein used in the present invention and preferably has the property equivalent to that of the protein used in the present invention (page 11, lines 12-15). Finally, the specification teaches the peptides which are preferably used include peptides having sequences of at least 20, preferably at least 50, more preferably at least 70, much more preferably at least 100, and most preferably at least 200 amino acids, in the constituent amino acid sequence of the protein used in the present invention, and the like (page 11, lines 15-20).

However, Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from SEQ ID NO:1 while retaining the ability of the claimed SGLT polypeptide homolog to transport glucose as disclosed in Example 8 and 9.

Working Examples

Although Applicants have provided examples for the biological activities for the full-length amino acid sequence of SEQ ID NO: 1 (Example 1 of glucose uptake-suppressing action by phlorizin; Example 2: analysis of the distribution expressed SGLT homolog in human gastrointestinal tract; Example 3: expression analysis of SGLT1 and the SGLT homolog in normal human small intestine epithelial cells in primary culture; Example 4: immunostaining of human small intestine slices with anti-human SGLT homolog antibody; Example 5: change in expression of the SGLT homolog in diabetic animal; Example 6: expression of the SGLT homolog in the small intestines from human, mouse rat hamster and monkey; Example 7: determination of glucose uptake level in the mouse, rat, and hamster small intestines by the organ culture system; Example 8: study of substrate specificity for SGLT1 and the SGLT homolog; Example 9: kinetic analysis of glucose uptake mediated by SGLT1 or the SGLT homolog; Example 11: determination of glucose uptake level mediated by the hamster SGLT), the specification does not provide any methods or working examples with all possible SGLT homologs and any derivatives, variants, or fragments for the amino acid sequence of SEQ ID NO:1.

The quantity of experimentation needed

Without sufficient disclosure in the specification, it would require undue experimentation for one of skill in the art to be able to make/use any SGLT homolog and any derivatives, variants, and fragments of the amino acid sequence of SEQ ID NO:1. In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to any SGLT homolog and any derivatives, variants, and fragments of the amino acid sequence of SEQ ID NO:1.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants have amended Claim 22 and, as such, respectfully disagree. The claims have been amended such that the the SGLT homolog is limited to a protein which comprises the amino acid sequence represented by SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID

NO: 50, or an amino acid sequence having at least about 90% homology to the amino acid sequence represented by SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 50, its partial peptide, or a salt thereof. Furthermore, the claimed method has been amended to recite specific steps as shown in the attached sheet. Support for the amendment can be found at, for example, pages 36-37. New claim 49, which depends from claim 22, has been added to more specifically limit the claimed method.

4. Claims 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> The Examiner states, "Claim 22 recites a method of screening a compound that regulates the glucose uptake activity of a Na+/glucose transporter (SGLT) homolog but the claim does not teach any active steps. The claim is incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination.

Applicants have amended Claim 22 and as currently amended do recite the essential steps required for a method of screening a compound that regulates the glucose uptake activity of a Na+/glucose transporter (SGLT) homolog. Applicants respectfully request reconsideration.

5. Claims 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Iwamoto et al. (WO 02/053738; priority to the publication date of July 11, 2002, cited in the IDS filed 04/28/2005).

> The Examiner states, "Iwamoto et al., (2002) teach a method of screening a compound regulating glucose uptake activity using the homolog (page 36, lines 19-29) meeting the limitations of claim 22.
>
> Furthermore, Iwamoto et al. (2002) recite that the method of screening a compound comprises SEQ ID NO:1 (abstract page 1 and page 1 of sequence listing), which has 100% homology with SEQ ID NO: 1 of the

instant application (see alignment in Exhibit A) meeting the limitations of claim 23.

Claims 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Thornton et al. (WO 01/92304 A2; priority to the publication date of May 25, 2001).

Thornton et al., (2001) teach a method of screening a compound regulating glucose uptake activity using the homolog (page 16, lines 1-9) meeting the limitations of claim 22.

Furthermore, Thornton et al (2001) recite that the method of screening a compound comprises SEQ ID NO:20 (page 16, line 3 and page 31 of sequence listing), which has 97.6% homology with SEQ ID NO: 1 of the instant application (see alignment in Exhibit C) meeting the limitations of claim 23. It is noted that the Examiner has interpreted the phrases "a SGLT homolog" and " protein comprising essentially the same amino acid sequence..." in the instant claims as reading upon variants, derivatives, and fragments of a SGLT homolog or the amino acid sequence of SEQ ID NO:1.

Claims 22 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Hu et al. (US 2003/0027301 A1; priority to the publication date of February 6, 2003).

Hu et al. teach a method of screening a compound (page 1, paragraph [0008]) regulating activity of a novel protein that shares structural similarity with sodium-glucose transporters (page 1, paragraph [0004]) and is expressed in the intestine (page 1 paragraph [0010]) meeting the limitations of claim 22. In addition, Hu et al. recite that the method includes the amino acid sequence SEQ ID NO:9 (page 25 of the sequence listing of US 2003/0027301 A1) that is 100% identical to the amino acid of SEQ ID NO:1 of the instant application (see alignment in Exhibit B attached to the instant Office Action) meeting the limitations of claim 23.

Applicants respectfully disagree. No references disclose, teach, or suggest a method of screening a compound or its salt that regulates the glucose uptake activity of a Na+/glucose (SGLT) homolog in the small intestine, and thus the present invention is novel and would not be obvious over the cited references. The present invention is based on the finding of the present inventors that the SGLT homolog is an important transporter for absorption of glucose in the small intestine (see page 3, lines 5-15 of the specification).

Applicants submit that the present application and Claims is in condition for allowance, and, accordingly, early consideration and allowance of the application is respectfully requested.

If for any reason an additional fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**. If the undersigned can be of any assistance in advancing the prosecution of this case, the Examiner is invited to contact him through the information given below.

Dated: September 24, 2007

Respectfully submitted,

By _____
Gregory B. Butler, Ph.D., Esq.
Registration No.: 34,558
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5595
Attorneys/Agents For Applicant

Attachment

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